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CLINICAL RESEARCH

Association of Social Isolation and Loneliness With Incident Heart Failure in a Population-Based Cohort Study

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ABSTRACT

BACKGROUND Social isolation and loneliness have emerged as important risk factors for cardiovascular diseases, particularly during the coronavirus disease pandemic. However, it is unclear whether social isolation and loneliness had independent and joint associations with incident heart failure (HF).

OBJECTIVES This study sought to examine the association of social isolation, loneliness, and their combination with incident HF.

METHODS The UK Biobank study is a population-based cohort study. Social isolation and loneliness were assessed using self-reported questionnaires. HF cases were identified by linking hospital records and death registries. The weighted polygenic risk score associated with HF was calculated.

RESULTS Among the 464,773 participants (mean age: 56.5 ± 8.1 years, 45.3% male), 12,898 incident HF cases were documented during a median follow-up of 12.3 years. Social isolation (most vs least: adjusted HR: 1.17; 95% CI:1.11-1.23) and loneliness (yes vs no: adjusted HR: 1.19; 95% CI: 1.11-1.27) were significantly associated with an increased risk of incident HF. The association between an elevated risk of HF and social isolation was modified by loneliness ($P_{interaction} = 0.034$). A gradient of association between social isolation and the risk of incident HF was found only among individuals without loneliness ($P_{trend} < 0.001$), but not among those with loneliness ($P_{trend} = 0.829$). These associations were independent of the genetic risk of HF.

CONCLUSIONS Social isolation and loneliness were independently associated with a higher likelihood of incident HF regardless of genetic risk. The association between social isolation and incident HF was potentially modified by loneliness status. (J Am Coll Cardiol HF 2023;11:334–344) © 2023 by the American College of Cardiology Foundation.

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Heart failure (HF) has emerged as a global pandemic affecting >60 million individuals worldwide.[1] Social isolation and loneliness have been recently recognized as important psychosocial determinants of cardiovascular diseases (CVDs), especially during the COVID-19 pandemic.[2,3] "Social isolation" refers to being objectively alone or having infrequent social connections, whereas "loneliness" is defined as a painful feeling caused by a discrepancy between one's desire for connections and the actual degree of connections.[4,5] Despite compelling evidence linking social isolation and loneliness to multiple cardiovascular outcomes and premature mortality, less is known about their association with HF.

Limited evidence has supported a link between social isolation and incident HF, with inconclusive evidence.[3,6,7] Loneliness was showed to outweigh social isolation in increasing cardiovascular risk.[8] However, whether loneliness also contributes to the development of HF is uncertain. Moreover, social isolation and loneliness are 2 weakly correlated but independent aspects of social disconnection,[9] suggesting that simply increasing objective social contact may not mitigate the health risk from loneliness and vice versa. The joint effects of social isolation and loneliness on the risk of HF have not yet been studied. Additionally, because the development of HF is determined by both environmental stimuli and genetic risk,[10] it is unclear whether such associations are modified by genetic risk for HF.

To address these knowledge gaps, the present study aimed to investigate the independent and joint effects of social isolation and loneliness on incident HF in a population-based cohort study of >400,000 adults enrolled in the UK Biobank. In addition, we examined the potential modulatory effects of genetic risk on these associations.

METHODS

STUDY POPULATION. The UK Biobank is a large population-based cohort study enrolling >500,000 community-dwelling adults aged between 40 and 69 years at 22 assessment centers across the United Kingdom during 2006 and 2010.[11] Details of the study are publicly available from the UK Biobank website.[12] The participants were asked to complete multiple touchscreen computer-based questionnaires, record physical measurements, and provide biological samples. The Northwest Multicenter Research Ethics Committee approved the UK Biobank study, and all participants provided informed consent. A flowchart of the inclusion and exclusion criteria of this study and detailed descriptions of the patient selection process are presented in Supplemental Figure 1 and Supplemental Methods, Section 1.

ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular disease
DBP = diastolic blood pressure
HF = heart failure
SBP = systolic blood pressure
SNV = single-nucleotide variation

SOCIAL ISOLATION AND LONELINESS. The social isolation index was constructed from 3 questions that are similar to those of the validated Berkman-Syme social network index:[13] 1) contact with family/friends/groups: "How often do you visit friends or family or have them visit you?;" 2) contact with family/friends/groups: "Which of the following (sports club or gym, pub or social club, religious group, adult education class, other group activity) do you engage in once a week or more often?;" and 3) living alone: "Including yourself, how many people are living together in your household?" One point was assigned to each question, resulting in a total social isolation score ranging from 0 to 3. Social isolation was further classified into 3 levels according to the total score: a score of 0 indicated least isolation; 1 indicated moderate isolation; and 2 and 3 indicated most isolation.[14] Loneliness was assessed with the following 2 questions that were derived from the revised University of California, Los Angeles loneliness scale:[15] 1) "Do you often feel lonely?;" and 2) "How often are you able to confide in someone close to you?" Individuals were defined as being lonely if they had a total score of 2.[14] Detailed information for scoring methods of social isolation and loneliness is listed in Supplemental Methods, Section 2.

OUTCOMES. The primary outcome was the incidence of HF. Vital status was ascertained by linking hospital admission data and death registry records. Hospital admission data were obtained from Health Episode Statistics in England and Wales and Scottish

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Morbidity Records in Scotland. The details of the linked data are available online.[16] HF cases were ascertained when having a primary/secondary diagnosis (hospital admission records) or underlying/contributory cause of death (death register) with the International Classification of Diseases-10th Revision codes of I11.0, I13.0, I13.2, and I50 for HF classifications,[17] followed up to May 31, 2021.

GENETIC RISK SCORE WITH HF. The detailed methods of genotyping, quality control, and imputation in the UK Biobank have been published elsewhere.[18] Briefly, restricting to the participants of White ethnicity, we selected the 12 independent genetic variants (single-nucleotide variation [SNV]) associated with HF risk reported by a previous genome-wide association study (Supplemental Table 1). Based on the number of risk alleles, the selected SNV data in the UK Biobank were coded as 0, 1, and 2. Next, we employed the following formula used in a previous study[19] to calculate the genetic risk score, which was further classified into high (quintile 5), intermediate (quintile 2-4), and low (quintile 1) risk according to distribution: weighted genetic risk score = $(\beta_1 \times SNV_1 + \beta_2 \times SNV_2 + \ldots \beta_n \times SNV_n) \times$ (n/sum of the β coefficients).

ASSESSMENT OF COVARIATES. We considered the following characteristics as the potential covariates: age (<65/≥65 years); sex (male/female); ethnicity (White/others); assessment center (England/Scotland/Wales); current employment status (employed/unemployed); education (college or university degree/noncollege or nonuniversity degree); Townsend deprivation index (continuous, a higher score indicates a higher degree of deprivation); smoking status (never/current/past); alcohol consumption status (abstainer/light or moderate drinker/heavy or abusive drinker); physical activity (continuous, metabolic equivalent task—sum of days performing walking, moderate, and vigorous activity); TV watching time (continuous, h/d); healthy diet score (continuous, 0-5 points); self-reported sleep duration (short: ≤6 h/d, normal: 7-8 h/d, long: ≥9 h/d); body mass index (continuous, kg/m^2); grip strength (kg); systolic blood pressure ([SBP], continuous, mm Hg), diastolic blood pressure ([DBP], continuous, mm Hg); pulse rate (continuous, beats/min), history of any chronic disease (having any diagnosis of diabetes mellitus; CVDs; cancer; and other long-standing illnesses, disability, or infirmity at baseline);[20] antihypertensive medication use (yes/no); antidiabetic medication use (yes/no); and statin use (yes/no). Detailed information is provided in Supplemental Methods, Section 3 and Supplemental Table 2.

STATISTICAL ANALYSIS. Baseline characteristics were summarized as proportions for categorical variables and mean ± SD or median (IQR) for continuous variables, as appropriate. Missing data were multiply imputed using the "mice" R package to minimize the potential for inferential bias. We followed up the included individuals until the date of the first diagnosis of HF, death, or censorship, whichever came first.

Cox proportional hazards regression was used to estimate the HRs and 95% CIs for the associations: model 1 adjusted for age and sex; model 2 additionally adjusted for socioeconomic status, lifestyle factors, and physical measurements; and model 3 additionally adjusted for health conditions and medication use. We also calculated the population-attributable fractions, which estimate the proportion of the risk of developing events in the study population that hypothetically would have been avoided or postponed from exposure. Once we observed a potential interaction between social isolation and loneliness using the variable cross-product term, stratified analyses according to the status of social isolation or loneliness were performed. Joint analyses were performed to directly compare groups with different levels of social isolation and loneliness against those who were least isolated and did not experience loneliness. Gene-environment interactions were tested using the same methods.

Several sensitivity analyses were conducted to assess the robustness of the results. First, we repeated the analyses in the sample with imputed missing exposure data. Second, to minimize the potential influence of reverse causality, we performed time-lag analyses by excluding cases of HF occurring within the first 2 years of enrollment. We then restricted the sample to participants with any diagnosis of ischemic heart disease or cardiomyopathy at baseline, and to patients with both incident HF and any ischemic heart disease or cardiomyopathy newly occurring before the onset of HF, respectively. We used the Fine-Gray subdistribution hazard model to assess the competing risk of death. Subgroup analyses for the main analyses were then performed to examine interactions between exposure and some important covariates. Finally, causal mediation analyses[21] were used to investigate the proportion of the exposure-outcome association mediated by of intermediate CVDs and diabetes, which occurred between baseline and the onset date of HF ("mediation"

R package).[22] To recover correct CIs for the estimates, the mediation analyses were estimated via bootstrapping (2,000 replications). Supplemental Methods, Section 4 displays the detailed description of the mediation analysis.

The proportional hazards assumptions were verified using graphical inspection of log-minus-log plots, indicating no substantial departures.[23] Statistical tests were 2-sided with $P < 0.05$ indicating statistical significance. All statistical analyses were performed using the R software (version 3.6.0).

RESULTS

The characteristics of the study sample were comparable to those of the overall sample in the UK Biobank (Supplemental Table 3). The study sample for the main analysis comprised 464,773 participants (mean age: 56.5 ± 8.1 years, 45.3% male), of whom 187,817 (40.4%) were moderately isolated, 66,545 (14.3%) were most isolated, and 22,208 (4.8%) had feelings of loneliness (**Table 1**). Over a median follow-up of 12.3 years (IQR: 11.5-13.0 years), 12,898 participants (13.0%) developed HF. Participants with a higher level of social isolation or loneliness were more likely to be men and have more unhealthy lifestyle factors, including smoking, physical inactivity, unhealthy sleep, a higher percentage of obesity, history of chronic diseases such as ischemic heart disease, and diabetes (**Table 1**). Similarly, the participants with incident HF have more unhealthy factors, a higher percentage of obesity, and history of chronic diseases (Supplemental Table 4).

As shown in **Table 2**, the most socially isolated participants, compared with the least isolated, had a greater risk of developing HF after adjusting for age and sex (model 1; HR: 1.54; 95% CI: 1.46-1.61), but this association was attenuated after additional adjustment for socioeconomic status, lifestyle factors, health conditions, and medication use (model 3; HR: 1.17; 95% CI: 1.11-1.23). Similarly, the HR of loneliness on incident HF was 1.69 (95% CI: 1.59-1.81) when adjusted for age and sex and attenuated to 1.19 (95% CI: 1.11-1.27) when further adjusted for socioeconomic status, lifestyle factors, health conditions, and medication use. The population-attributable fraction analyses indicated that 6.12% (95% CI: 4.06%-8.18%) and 1.26% (95% CI: 0.75%-1.78%) of incident cases of HF during follow-up in this population could have been prevented if all individuals had been the least socially isolated or had no loneliness, respectively. Among all the items, living alone contributed to the greatest risk of incident HF (HR: 1.21; 95% CI: 1.16-1.26; population-attributable fraction: 4.66%). The associations of social isolation and loneliness with incident HF displayed a dose-response relationship, as shown in the Kaplan-Meier curves (Supplemental Figures 2 and 3). There were dose-gradient associations between the continuous scores of social isolation and loneliness and the likelihood of incident HF (both $P_{trend} < 0.001$) (Supplemental Table 5).

Social isolation and loneliness interacted with the subsequent risk of HF ($P_{interaction} = 0.034$) (**Table 3**). When stratified by loneliness status, there was a gradient association between social isolation and the risk of incident HF among individuals without loneliness ($P_{trend} < 0.001$), but not among those with loneliness ($P_{trend} = 0.829$) (**Table 3**). When stratified by social isolation level, the association of loneliness with incident HF remained significant only among the least and moderately isolated groups (both $P_{trend} < 0.001$), but not among the most isolated groups ($P_{trend} = 0.508$) (Supplemental Table 6). **Figure 1** shows the joint association of social isolation and loneliness with incident HF, with the reference group being those who were least isolated and not lonely. These patterns were consistent with those of the stratified analyses. An increasing trend in HRs was observed following an increasing level of social isolation in the group without loneliness, whereas the HRs were rather identical in the loneliness subgroup.

Genetic predisposition to HF did not modify the association of social isolation ($P_{interaction} = 0.881$) or loneliness ($P_{interaction} = 0.774$) with the risk of incident HF (data not shown). The joint and stratified analyses collectively showed that both social isolation and loneliness were significantly associated with an increased risk of incident HF within each group with low, intermediate, and high genetic risks for HF (**Figure 2,** Supplemental Table 7).

The major results remained robust in all sensitivity analyses including the analysis of the sample with imputed data (Supplemental Tables 8 to 10), the time-lag analysis performed by excluding HF cases that occurred within the first 2 years of follow-up (Supplemental Tables 11 to 13), the analysis performed after excluding participants with a diagnosis of ischemic heart disease and cardiomyopathy at baseline (Supplemental Tables 14 to 16), the analysis excluding cases wherein both incident HF and any ischemic heart disease or cardiomyopathy newly occurred before the onset of HF (Supplemental Tables 14 to 16), and the analysis using the Fine-Gray models accounting for a competing risk of death (Supplemental Table 17). The interactive effects between social isolation or loneliness and most covariates were lacking (all $P_{interaction} > 0.05$)

TABLE 1 Baseline Characteristics of Participants in the UK Biobank by Social Isolation and Loneliness Status

		Social Isolation			Loneliness	
	Total (N = 464,773)	Least Isolated (n = 210,411)	Moderately Isolated (n = 187,817)	Most Isolated (n = 66,545)	No Loneliness (n = 442,565)	Loneliness (n = 22,208)
Age, y	56.5 ± 8.1	56.8 ± 8.1	56.3 ± 8.1	56.0 ± 7.9	56.5 ± 8.1	55.9 ± 7.9
<65	377,298 (81.2)	168,643 (80.1)	152,999 (81.5)	55,656 (83.6)	358,729 (81.1)	18,569 (83.6)
≥65	87,475 (18.8)	41,768 (19.9)	34,818 (18.5)	10,889 (16.4)	83,836 (18.9)	3,639 (16.4)
Male	210,405 (45.3)	93,030 (44.2)	84,046 (44.7)	33,329 (50.1)	199,157 (45.0)	11,248 (50.6)
Ethnicity, White	443,302 (95.4)	202,425 (96.2)	178,645 (95.1)	62,232 (93.5)	422,426 (95.4)	20,876 (94.0)
Assessment center						
England	411,545 (88.5)	185,533 (88.2)	166,613 (88.7)	59,399 (89.3)	392,042 (88.6)	19,503 (87.8)
Scotland	33,664 (7.2)	15,485 (7.4)	13,476 (7.2)	4,703 (7.1)	31,970 (7.2)	1,694 (7.6)
Wales	19,564 (4.2)	9,393 (4.5)	7,728 (4.1)	2,443 (3.7)	18,553 (4.2)	1,011 (4.6)
Currently employed	271,967 (58.5)	118,608 (56.4)	112,234 (59.8)	41,125 (61.8)	259,964 (58.7)	12,003 (54.0)
College or university degree	154,342 (33.2)	70,278 (33.4)	61,671 (32.8)	22,393 (33.7)	149,044 (33.7)	5,298 (23.9)
Townsend deprivation index[a]	−1.4 ± 3.0	−1.8 ± 2.8	−1.2 ± 3.1	−0.4 ± 3.4	−1.4 ± 3.0	−0.4 ± 3.5
Current smoker	48,460 (10.4)	16,750 (8.0)	20,947 (11.2)	10,763 (16.2)	44,467 (10.0)	3,993 (18.0)
Alcohol consumption status						
Abstainer	53,233 (11.5)	18,960 (9.0)	22,925 (12.2)	11,348 (17.1)	49,573 (11.2)	3,660 (16.5)
Light or moderate drinker	308,291 (66.3)	142,267 (67.6)	124,412 (66.2)	41,612 (62.5)	294,740 (66.6)	13,551 (61.0)
Heavy or abusive drinker	103,249 (22.2)	49,184 (23.4)	40,480 (21.6)	13,585 (20.4)	98,252 (22.2)	4,997 (22.5)
Physical activity, METs	10.6 ± 4.8	11.1 ± 4.7	10.4 ± 4.9	9.7 ± 5.0	10.6 ± 4.8	10.0 ± 5.2
TV watching time, h/d	2.8 ± 1.7	2.7 ± 1.5	2.8 ± 1.7	3.0 ± 2.0	2.8 ± 1.6	3.3 ± 2.2
Healthy diet score	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)
Sleep duration						
Normal, 7-8 h/d	315,665 (67.9)	148,825 (70.7)	125,652 (66.9)	41,188 (61.9)	303,798 (68.6)	11,867 (53.4)
Short, <7 h/d	113,617 (24.4)	45,607 (21.7)	48,098 (25.6)	19,912 (29.9)	105,219 (23.8)	8,398 (37.8)
Long, >8 h/d	35,491 (7.6)	15,979 (7.6)	14,067 (7.5)	5,445 (8.2)	33,548 (7.6)	1,943 (8.7)
Body mass index, kg/m^2	27.4 ± 4.8	27.3 ± 4.5	27.5 ± 4.9	27.7 ± 5.2	27.4 ± 4.7	28.5 ± 5.5
Nonobese	352,048 (75.7)	162,799 (77.4)	140,928 (75.0)	48,321 (72.6)	337,088 (76.2)	14,960 (67.4)
Obese	112,725 (24.3)	47,612 (22.6)	46,889 (25.0)	18,224 (27.4)	105,477 (23.8)	7,248 (32.6)
Grip strength, kg	30.7 ± 11.0	30.8 ± 10.9	30.5 ± 11.1	30.8 ± 11.1	30.7 ± 11.0	30.2 ± 11.3
SBP, mm Hg	140 ± 20	140 ± 20	140 ± 20	140 ± 20	140 ± 20	139 ± 19
DBP, mm Hg	82 ± 11	82 ± 11	82 ± 11	83 ± 11	82 ± 11	82 ± 11
Pulse rate, beats/min	70 ± 12	69 ± 12	70 ± 12	71 ± 12	70 ± 12	71 ± 12
History of any chronic disease[b]	191,362 (41.2)	81,760 (38.9)	78,679 (41.9)	30,923 (46.5)	179,410 (40.5)	11,952 (53.8)
History of myocardial infarction	5,372 (1.2)	2,345 (1.1)	2,147 (1.1)	880 (1.3)	4,955 (1.1)	417 (1.9)
History of ischemic heart disease	17,156 (3.7)	7,522 (3.6)	6,833 (3.6)	2,801 (4.2)	15,839 (3.6)	1,317 (5.9)
History of cardiomyopathy	344 (0.1)	145 (0.1)	147 (0.1)	52 (0.1)	322 (0.1)	22 (0.1)
History of diabetes	7,926 (1.7)	2,886 (1.4)	3,377 (1.8)	1,663 (2.5)	7,166 (1.6)	760 (3.4)
Antihypertensive medication use	95,447 (20.5)	42,019 (20.0)	38,763 (20.6)	14,665 (22.0)	90,067 (20.4)	5,380 (24.2)
Antidiabetic medication use	16,613 (3.6)	6,237 (3.0)	7,001 (3.7)	3,375 (5.1)	15,219 (3.4)	1,394 (6.3)
Statin use	70,369 (15.1)	31,069 (14.8)	28,374 (15.1)	10,926 (16.4)	66,214 (15.0)	4,155 (18.7)

Values are mean ± SD, n (%), or median (IQR). [a]Positive values of the index will indicate areas with high material deprivation, whereas those with negative values will indicate relative affluence. [b]History of any chronic disease refers to having any diagnosis of diabetes, cardiovascular diseases, cancer, or other long-standing illnesses; disability; or infirmity at baseline.

DBP = diastolic blood pressure; SBP = systolic blood pressure.

(Supplemental Figure 4), suggesting that these covariates did not modify the associations of social disconnection with incident HF. Social isolation and loneliness seemed to have similar associations with incident HF across younger (<65 years) and older (≥65 years) groups, but show stronger associations with incident HF among women than men (social isolation × sex: $P_{interaction}$ = 0.004, loneliness × sex: $P_{interaction}$ = 0.079) (Supplemental Figure 4, Supplemental Tables 18 to 21).

In causal mediation analyses, 41% (95% CI: 19%-59%) and 25% (95% CI: 8%-43%) of the association between social isolation and incident HF was significantly mediated by newly occurring cardiac events (ischemic heart disease and cardiomyopathy) and diabetes mellitus, respectively; 63% (95% CI: 40%-90%) and 41% (95% CI: 22%-74%) of the association between loneliness with incident HF was mediated by newly occurring cardiac events and diabetes mellitus, respectively (Supplemental Table 22).

TABLE 2 Associations of Social Isolation and Loneliness With Subsequent Risk for Incident HF

	n	Cases/Person-Years	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)	PAF (%)[c]
Social isolation						6.12
Least isolated	210,411	5,163/2,524,465	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	
Moderately isolated	187,817	5,400/2,236,403	1.22 (1.18-1.27)	1.11 (1.06-1.15)	1.09 (1.05-1.13)	
Most isolated	66,545	2,335/781,542	1.54 (1.46-1.61)	1.19 (1.13-1.25)	1.17 (1.11-1.23)	
Items of social isolation						
Contact with family/ friends/groups						1.30
More	260,599	6,983/3,117,798	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	
Little	204,174	5,915/2,424,611	1.15 (1.11-1.19)	1.04 (1.01-1.08)	1.03 (0.99-1.07)	
Live alone						4.66
No	378,782	9,561/4,533,519	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	
Yes	85,991	3,337/1,008,891	1.55 (1.49-1.61)	1.22 (1.17-1.27)	1.21 (1.16-1.26)	
Loneliness						1.26
No	442,565	11,929/5,280,749	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	
Yes	22,208	969/261,661	1.69 (1.59-1.81)	1.25 (1.17-1.33)	1.19 (1.11-1.27)	
Items of loneliness						
Lonely						2.34
No	379,164	10,037/4,527,718	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	
Yes	85,609	2,861/1,014,691	1.51 (1.45-1.57)	1.17 (1.12-1.22)	1.11 (1.07-1.16)	
Able to confide						2.38
Usually	396,836	10,230/4,738,380	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	
Never/almost never	67,937	2,668/804,029	1.34 (1.28-1.40)	1.14 (1.09-1.19)	1.13 (1.08-1.18)	

[a]Model 1 adjusted for age and sex. [b]Model 2 additionally adjusted for ethnicity, assessment center, current employment status, education level, Townsend deprivation index, smoking status, alcohol consumption status, physical activity, TV watching time, healthy diet score, sleep duration, obesity, grip strength, systolic blood pressure, diastolic blood pressure, and pulse rate. [c]Model 3 additionally adjusted for history of any chronic disease, antihypertensive medication use, antidiabetic medication use, and statin use.

HF = heart failure; PAF = population-attributable fraction; Ref. = reference.

DISCUSSION

In this population-based study of >400,000 middle-aged and older adults in the UK Biobank, we obtained several noteworthy findings (Central Illustration). First, both social isolation and loneliness increased the risk of incident HF approximately 15%-20% in a dose-dependent manner. Second, social isolation and loneliness showed significant interaction effects on HF risk. The dose-gradient risk for incident HF caused by social isolation was only found among individuals without loneliness but not among those with loneliness. In addition, the associations between social isolation and loneliness and incident HF were independent of the genetic risk of HF.

TABLE 3 Risk of Incident HF According to Social Isolation Within Each Loneliness Category

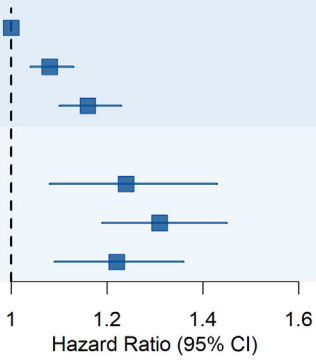
	No Loneliness			Loneliness		
	n	Cases/Person-Years	HR (95% CI)[a]	n	Cases/Person-Years	HR (95% CI)[a]
Social isolation						
Least isolated	204,837	4,968/2,457,793	1.00 (Ref.)	5,574	195/66,671	1.00 (Ref.)
Moderately isolated	178,314	4,979/2,124,097	1.08 (1.04-1.13)	9,503	421/112,306	1.06 (0.89-1.26)
Most isolated	59,414	1,982/698,858	1.16 (1.10-1.23)	7,131	353/82,684	1.00 (0.83-1.20)
P_{trend}			<0.001			0.829
$P_{interaction}$[b]						0.034

[a]HRs were adjusted for age, sex, ethnicity, assessment center, current employment status, education level, Townsend deprivation index, smoking status, alcohol consumption status, physical activity, TV watching time, healthy diet score, sleep duration, obesity, grip strength, systolic blood pressure, diastolic blood pressure, pulse rate, history of any chronic disease, antihypertensive medication use, antidiabetic medication use, and statin use. [b]*P* value for interaction of social isolation and loneliness with incident HF in the multivariable Cox model.

Abbreviation as in Table 2.

FIGURE 1 Joint Associations of Social Isolation and Loneliness With Incident HF

Subgroup	N	Cases/person-Years	Hazard Ratio (95%CI)	*P* value
No loneliness				
Least isolated	204,837	4,968/2,457,793	1.00 [Reference]	
Moderate isolated	178,314	4,979/2,124,097	1.08 (1.04-1.13)	<0.001
Most isolated	59,414	1,982/698,858	1.16 (1.10-1.23)	<0.001
Loneliness				
Least isolated	5,574	195/66,671	1.24 (1.08-1.43)	0.003
Moderate isolated	9,503	421/112,306	1.31 (1.19-1.45)	<0.001
Most isolated	7,131	353/82,684	1.22 (1.09-1.36)	0.001



HRs were adjusted for age, sex, ethnicity, assessment center, current employment status, education level, Townsend deprivation index, smoking status, alcohol consumption status, physical activity, TV watching time, healthy diet score, sleep duration, obesity, grip strength, systolic blood pressure, diastolic blood pressure, pulse rate, history of any chronic disease, antihypertensive medication use, antidiabetic medication use, and statin use. HF = heart failure.

Our findings help complement the broad spectrum of published reports on associations of social relationships with CVD risk. A previous cohort study uncovered a potential link between social disconnection and incident HF but it only considered social isolation.[6] Several recent studies showed that both aspects of social disconnection,[20,24,25] social isolation only,[7] or loneliness only[8,26] were associated with the risk of incident CVD. These inconsistent findings were possibly caused by the variations in social network measurements,[3] age group,[7] sample size, and definition of the CVD across these studies. Our study offsets the limitations of some previous studies, such as having a limited number of HF events[7] or lack of direct comparisons of social isolation and loneliness in the same study setting.[6] In addition, we are the first to reveal that associations of social isolation and loneliness with incident HF persisted irrespective of genetic risk, which is consistent with a prior gene-interaction study.[17]

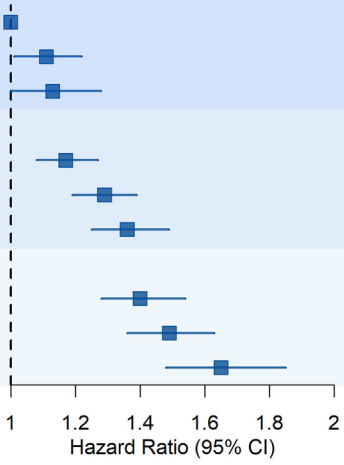
In addition, we documented that the association between social isolation and incident HF depended on loneliness status. Consistently, the impact of subjective social disconnection on incident CVDs[8] and mental health outcomes[27] was reported to be more important than that of objective disconnection. Loneliness can exist regardless of one's objective social connections and the time that they are socially isolated from others.[4,27] Loneliness is likely a stronger psychological stressor than social isolation,[28] because loneliness is common in individuals who are hostile or have stressful social relationships[29] and bridges the link between social isolation and depression.[27] Another possible explanation was that loneliness might be more closely correlated with the CVD precursors of HF. This was supported by our finding that nonfatal CVDs more substantially mediated the association of loneliness with incident HF. Conversely, social isolation showed a stronger association with fatal CVDs, possibly because of a lack of emergency assistance,[14,20] suggesting that socially isolated individuals may have died of fatal diseases before they could be hospitalized for HF.

We speculate several potential mechanisms to explain the association of social isolation and loneliness with incident HF. First, as speculated previously, traditional risk cardiovascular factors, unhealthy lifestyles, and intermediate chronic diseases may serve as mediators or moderators.[30] We found that the estimated associations were substantially attenuated after controlling for these factors and that the cardiac diseases and diabetes newly occurring before the onset of HF largely mediated the associations, which supported this speculation. Third, social disconnection may largely restrict older adults from getting social support or seeking health care and resources, ultimately resulting in poor management of risk factors or chronic diseases preceding HF. Finally, excess risk from social isolation and loneliness remained unexplained, suggesting some biological pathways beyond the known

FIGURE 2 **Joint Associations of Social Isolation, Loneliness, and Genetic Risk With Incident HF**

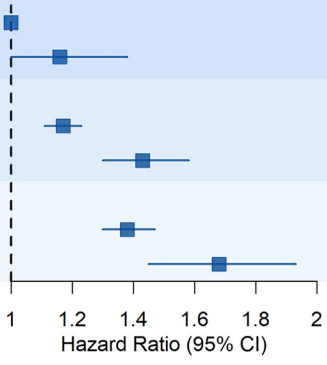
A

Subgroup	N	Cases/person-Years	Hazard Ratio (95%CI)	*P* value
Low genetic risk				
Least isolated	39,711	813/478,136	1.00 [Reference]	
Moderate isolated	34,979	860/418,606	1.11 (1.01-1.22)	0.032
Most isolated	11,905	342/140,401	1.13 (1.00-1.28)	0.058
Intermediate genetic risk				
Least isolated	118,544	2,879/1,424,629	1.17 (1.08-1.27)	<0.001
Moderate isolated	103,936	2,979/1,239,869	1.29 (1.19-1.39)	<0.001
Most isolated	36,346	1,274/427,983	1.36 (1.25-1.49)	<0.001
High genetic risk				
Least isolated	39,193	1,156/469,545	1.40 (1.28-1.54)	<0.001
Moderate isolated	35,023	1,193/416,092	1.49 (1.36-1.63)	<0.001
Most isolated	11,971	520/140,100	1.65 (1.48-1.85)	<0.001



B

Subgroup	N	Cases/person-Years	Hazard Ratio (95%CI)	*P* value
Low genetic risk				
No loneliness	82,450	1,867/988,072	1.00 [Reference]	
Loneliness	4,145	148/49,072	1.16 (0.98-1.38)	0.075
Intermediate genetic risk				
No loneliness	246,725	6,582/2,949,585	1.17 (1.11-1.23)	<0.001
Loneliness	12,101	550/142,896	1.43 (1.30-1.58)	<0.001
High genetic risk				
No loneliness	82,236	2,658/979,383	1.38 (1.30-1.47)	<0.001
Loneliness	3,951	211/46,354	1.68 (1.45-1.93)	<0.001

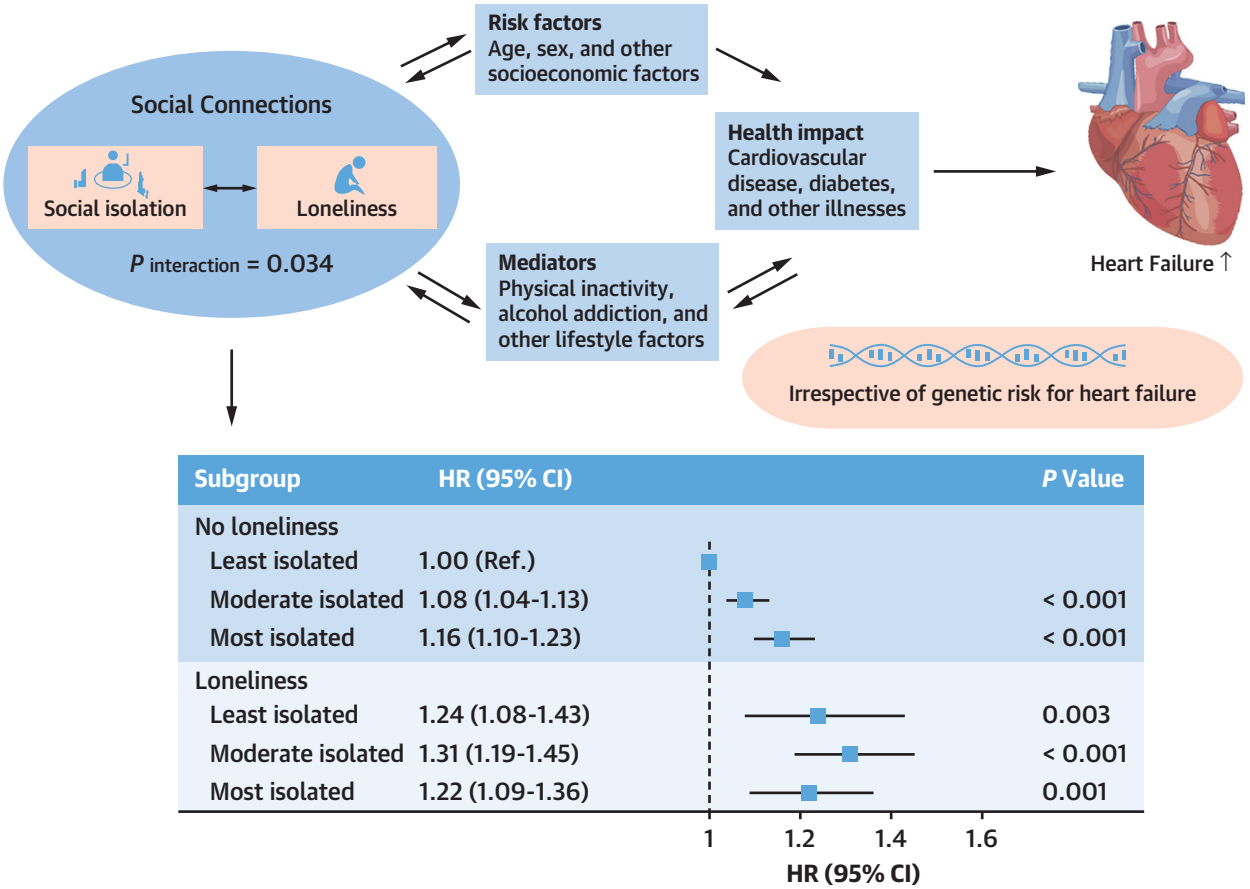


(A) Social isolation; **(B)** loneliness. HRs were adjusted for age, sex, ethnicity, assessment center, current employment status, education level, Townsend deprivation index, smoking status, alcohol consumption status, physical activity, TV watching time, healthy diet score, sleep duration, obesity, grip strength, systolic blood pressure, diastolic blood pressure, pulse rate, history of any chronic disease, antihypertensive medication use, antidiabetic medication use, and statin use. Abbreviation as in **Figure 1**.

predecessors of HF. For instance, social isolation and loneliness are associated with increased activity of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system,[31] enhanced inflammation, and oxidative stress.[32] These changes may accelerate atherosclerosis and increase peripheral pressure,[32] which in turn, may promote the development of cardiac remodeling preceding HF. As suggested by a recent genome-wide association study, showing strong genetic heritability of social connection, genetic basis is also likely to account for the effects of social isolation and loneliness on the cardiovascular system.[33]

From a public health perspective, our findings highlight the need for future investigations of effective tools to screen for social isolation and loneliness, in addition to traditional HF risk factors, in routine clinical care to inform future HF risk. A systematic approach across the individual, communal, and societal levels should be implemented to alleviate the burden of social isolation and loneliness.[5,29] Individual-level strategies could include

CENTRAL ILLUSTRATION Association of Social Isolation, Loneliness, and Genetic Risk With Incident Heart Failure



Liang YY, et al. J Am Coll Cardiol HF. 2023;11(3):334-344.

HRs were adjusted for age, sex, ethnicity, assessment center, current employment status, education level, Townsend deprivation index, smoking status, alcohol consumption status, physical activity, TV watching time, healthy diet score, sleep duration, obesity, grip strength, systolic blood pressure, diastolic blood pressure, pulse rate, history of any chronic disease, antihypertensive medication use, antidiabetic medication use, and statin use. The heart icon is from Figdraw. Ref. = reference.

psychological therapies targeting negative coping, social skills training, and supported socialization.[29] For example, a recent trial showed that a layperson-delivered, empathy-oriented telephone call program within 4 weeks significantly reduced loneliness during the COVID-19 pandemic.[34] Alternatively, community-level strategies[29] and social and political policies[5] are also warranted to help incorporate interventions targeting social disconnection across diverse ethical and cultural settings. Finally, to help prevent HF, it is also important to develop therapeutic strategies to prevent subsequent mediators or moderators linking social disconnection to incident HF.

STUDY STRENGTHS AND LIMITATIONS. The strengths of this study include its large sample size, long-term follow-up, prospective study design, careful control of covariates, and comprehensive sensitivity analyses. However, this study had several limitations. First, the UK Biobank only assessed in-person contact as an indicator of social isolation. It lacks assessments of virtual connections or other aspects of social relationships. Second, the simple questions used to assess social isolation and loneliness in the UK Biobank have not been validated. However, these questions were adapted from validated scales[13,15] and widely adopted in previous studies.[14,20] Third, using hospital admission and death linkage methods to ascertain HF cases may exclude individuals with mild HF events. Therefore, the incidence of HF may have been underestimated in this study. Fourth, the

current study included a relatively young population and regarded HF as an outcome despite the long follow-up period of approximately 12 years, which may limit the generalizability of this study and result in a lower observed incidence of HF. The number of HF events in our study was still far larger than that in previous studies,[6,7] suggesting sufficient statistical power. Fifth, similar to other large-scale epidemiologic studies,[6,35] the present study failed to subclassify etiologic types and severity of HF because of a lack of ejection fraction information in the UK Biobank. In addition, a significant concern of this study was reverse causation. However, the results remained robust in the sensitivity analyses, suggesting that the observed associations were less likely to be confounded by reverse causality. Finally, most of the participants were of European descent in the UK Biobank; thus, the current findings should be cautiously applied to other ethnic groups.

CONCLUSIONS

The present study suggests that social isolation and loneliness could be associated with an increased risk of subsequent HF, regardless of the genetic risk profiles. Moreover, loneliness may modify the association between social isolation and HF incidence. Given regular social distancing during the COVID-19 pandemic, these findings suggest that the interventions across individual, communal, and societal levels to strengthen subjective and objective social connections could potentially hold promise for the maintenance of cardiovascular health.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Social isolation and loneliness are 2 important modifiable risk factors of incident HF, regardless of the genetic risk of HF. The association between social isolation and incident HF is potentially modified by feelings of loneliness.

TRANSLATIONAL OUTLOOK: Future research should develop effective and systemic interventions to reduce social isolation and loneliness and validate whether the improvement of social connection help reduce HF risk in later life, particularly considering the increasing incidence of social disconnection caused by the COVID-19 pandemic.

REFERENCES

1. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats A. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res*. 2022;118(17):3272–3287. https://doi.org/10.1093/cvr/cvac013

2. Escalante E, Golden RL, Mason DJ. Social isolation and loneliness: imperatives for health care in a post-COVID world. *JAMA*. 2021;325(6):520–521.

3. Cené CW, Beckie TM, Sims M, et al. Effects of objective and perceived social isolation on cardiovascular and brain health: a scientific statement from the American Heart Association. *J Am Heart Assoc*. 2022;11(16):e026493.

4. Blazer D. Social isolation and loneliness in older adults-a mental health/public health challenge. *JAMA Psychiatry*. 2020;77(10):990–991.

5. Prohaska T, Burholt V, Burns A, et al. Consensus statement: loneliness in older adults, the 21st century social determinant of health? *BMJ Open*. 2020;10:e034967.

6. Cené CW, Loehr L, Lin FC, et al. Social isolation, vital exhaustion, and incident heart failure: findings from the Atherosclerosis Risk in Communities Study. *Eur J Heart Fail*. 2012;14(7):748–753.

7. Freak-Poli R, Ryan J, Neumann JT, et al. Social isolation, social support and loneliness as predictors of cardiovascular disease incidence and mortality. *BMC Geriatr*. 2021;21(1):711.

8. Bu F, Zaninotto P, Fancourt D. Longitudinal associations between loneliness, social isolation and cardiovascular events. *Heart*. 2020;106:1394–1399.

9. Coyle CE, Dugan E. Social isolation, loneliness and health among older adults. *J Aging Health*. 2012;24(8):1346–1363.

10. Liew C-C, Dzau VJ. Molecular genetics and genomics of heart failure. *Nat Rev Genet*. 2004;5(11):811–825.

11. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol*. 2017;186(9):1026–1034.

12. Smiley A, King D, Bidulescu A. The association between sleep duration and metabolic syndrome: the NHANES 2013/2014. *Nutrients*. 2019;11(11):2582.

13. Berkman LF, Syme SL. Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda County residents. *Am J Epidemiol*. 1979;109(2):186–204.

14. Smith RW, Barnes I, Green J, Reeves GK, Beral V, Floud S. Social isolation and risk of heart

disease and stroke: analysis of two large UK prospective studies. *Lancet Public Health*. 2021;6(4):e232–e239.

15. Hughes ME, Waite LJ, Hawkley LC, Cacioppo JT. A short scale for measuring loneliness in large surveys: results from two population-based studies. *Res Aging*. 2004;26(6):655–672.

16. Wang J, Kwok MK, Au Yeung SL, et al. Sleep duration and risk of diabetes: observational and Mendelian randomization studies. *Prev Med*. 2019;119:24–30.

17. Wang M, Zhou T, Song Y, et al. Joint exposure to various ambient air pollutants and incident heart failure: a prospective analysis in UK Biobank. *Eur Heart J*. 2021;42(16):1582–1591.

18. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature*. 2018;562(7726):203–209.

19. Ripatti S, Tikkanen E, Orho-Melander M, et al. A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses. *Lancet*. 2010;376(9750):1393–1400.

20. Elovainio M, Hakulinen C, Pulkki-Råback L, et al. Contribution of risk factors to excess mortality in isolated and lonely individuals: an analysis of data from the UK Biobank cohort study. *Lancet Public Health*. 2017;2(6):e260–e266.

21. Tingley D, Yamamoto T, Hirose K, Keele LJ, Imai KJ. Mediation: R package for causal mediation analysis. *J Stat Softw*. 2014;59(5):1–38.

22. Wang W, Zhang MJ, Inciardi RM, et al. Association of echocardiographic measures of left atrial function and size with incident dementia. *JAMA*. 2022;327:1138–1148.

23. Grambsch PM. Goodness-of-fit and diagnostics for proportional hazards regression models. *Cancer Treat Res*. 1995;75:95–112.

24. Hakulinen C, Pulkki-Råback L, Virtanen M, Jokela M, Kivimäki M, Elovainio M. Social isolation and loneliness as risk factors for myocardial infarction, stroke and mortality: UK Biobank cohort study of 479 054 men and women. *Heart*. 2018;104(18):1536–1542.

25. Golaszewski NM, LaCroix AZ, Godino JG, et al. evaluation of social isolation, loneliness, and cardiovascular disease among older women in the US. *JAMA Netw Open*. 2022;5(2):e2146461.

26. Valtorta NK, Kanaan M, Gilbody S, Hanratty B. Loneliness, social isolation and risk of cardiovascular disease in the English Longitudinal Study of Ageing. *Eur J Prev Cardiol*. 2018;25(13):1387–1396.

27. Santini ZI, Jose PE, York Cornwell E, et al. Social disconnectedness, perceived isolation, and symptoms of depression and anxiety among older Americans (NSHAP): a longitudinal mediation analysis. *Lancet Public Health*. 2020;5(1):e62–e70.

28. Levine GN, Cohen BE, Commodore-Mensah Y, et al. Psychological health, well-being, and the mind-heart-body connection: a scientific statement from the American Heart Association. *Circulation*. 2021;143(10):e763–e783.

29. Holt-Lunstad J. Why social relationships are important for physical health: a systems approach to understanding and modifying risk and protection. *Annu Rev Psychol*. 2018;69:437–458.

30. National Academies of Sciences, Engineering, and Medicine. *Social Isolation and Loneliness in Older Adults: Opportunities for the Health Care System*. National Academies Press; 2020.

31. Cacioppo J, Cacioppo S, Capitanio J, Cole S. The neuroendocrinology of social isolation. *Annu Rev Psychol*. 2015;66:733–767.

32. Li H, Xia N. The role of oxidative stress in cardiovascular disease caused by social isolation and loneliness. *Redox Biol*. 2020;37:101585.

33. Day FR, Ong KK, Perry JRB. Elucidating the genetic basis of social interaction and isolation. *Nat Commun*. 2018;9(1):2457.

34. Kahlon MK, Aksan N, Aubrey R, et al. Effect of layperson-delivered, empathy-focused program of telephone calls on loneliness, depression, and anxiety among adults during the COVID-19 pandemic: a randomized clinical trial. *JAMA Psychiatry*. 2021;78(6):616–622.

35. Gustad LT, Laugsand LE, Janszky I, Dalen H, Bjerkeset O. Symptoms of anxiety and depression and risk of heart failure: the HUNT Study. *Eur J Heart Fail*. 2014;16(8):861–870.

KEY WORDS genetic predisposition to disease, heart failure, loneliness, social isolation, UK Biobank

APPENDIX For an expanded Methods section as well as supplemental figures, tables, and references, please see the online version of this paper.